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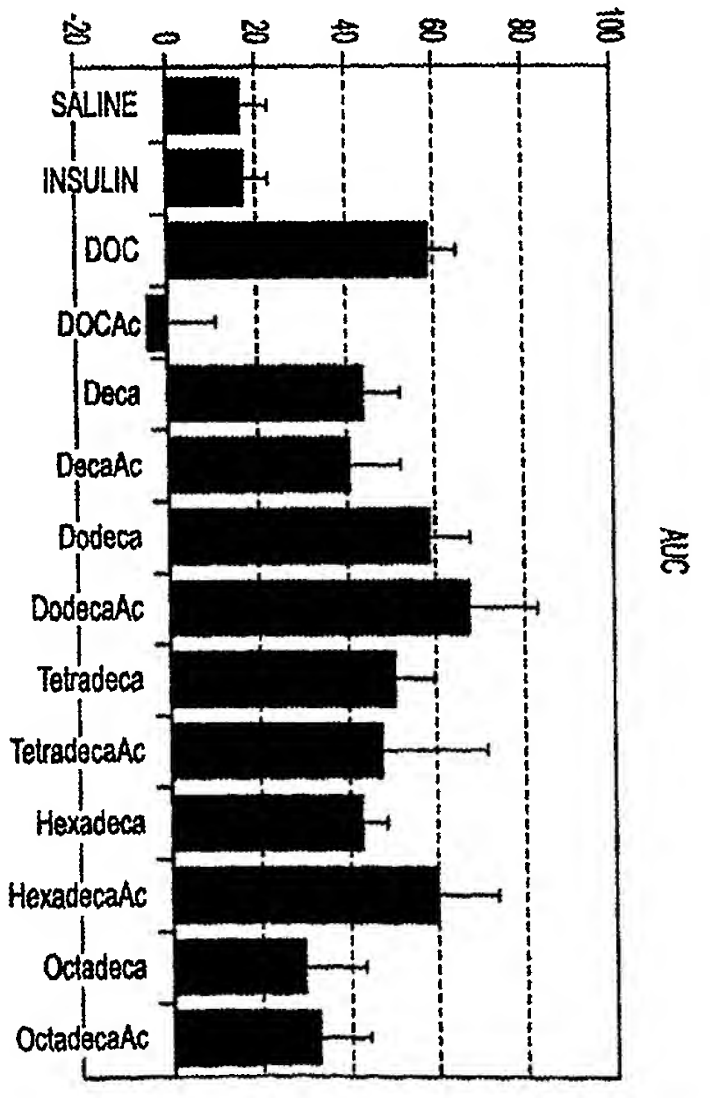
(54) Title: SYSTEMS FOR ORAL DELIVERY

(57) Abstract

A pharmaceutical or another, biologically active substance, for oral administration, can be "coated" or "encapsulated" with a carboxylic acid, such that the substance is protected from proteolysis in the stomach and is taken up from the intestine. It is thought that the carboxylic acids coat and protect the active agent from the proteolytic envrionment of the stomach, allowing the agent to pass safely through the stomach and to be absorbed in the small intestines. The carboxylic acid agent complex can be adopted for oral, nasal, buccal, and transdermal delivery of moderately soluluble and even insoluble bioactive agents.



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SYSTEMS FOR ORAL DELIVERY

BACKGROUND OF THE INVENTION

The present invention relates to carboxylic acid encapsulation systems useful for pharmaceutical delivery. In particular, the invention relates to improved methods of protecting pharmaceuticals from intestinal degradation. for enhancing the oral uptake of the pharmaceutical agent within a vertebrate host and for the delivery of insoluble and moderately soluble pharmaceutical agents, and biologically active pharmaceutical agents.

Delivery of a pharmaceutical agent to its site of action and controlling the rate of release of pharmaceutical agents are enduring problems in developing and improving pharmaceutical therapies. This is particularly a problem when the pharmaceutical to be delivered is administered orally to the target animal. In this regard, the gastro-intestinal tract of vertebrate animals provides a number of physical and chemical barriers against the successful administration of therapeutic agents. For example a therapeutic agent must be able to withstand the attack of endogenous enzymes such as trypsin, pepsin and chymotrypsin, as well as gastric acidity without losing activity. Once the pharmaceutical has survived these conditions it must still cross the gastrointestinal mucosa, enter the blood stream and move to the site where activity is required. Moreover, all of this must take place at an appropriate rate to ensure the correct therapeutic dosage is delivered. Thus, many compounds are ineffective or exhibit low or variable potency when administered orally. Despite these problems it is still preferable to administer biologically active agents orally, especially in terms of patient comfort, compliance, acceptability and cost.

In the past, a number of delivery technologies have been developed, which attempt to solve these problems. The simplest of these is the administration of a particularly high dose of active agent, with the hope that at least some of the agent reaches the desired active site without degradation. This approach to administration of enteric agents is, however problematic and generally not economical. An alternative approach has been the use of enteric coatings on tablets and gel formulation, with the

object of delaying the release of the encapsulated compound until it has left the harsh environment of the stomach, thereby avoiding some, but not all of the proteolytic enzymes present in the intestine. There also has been considerable research recently to develop liposomes or lipid microbubbles that can be used to encapsulate active agents which is described by Patel *et al.*, *FEBS Letters* 62: 60, (1979), and Hashimoto *et al.*, *Endocrinol. Japan* 26: 337 (1976). These approaches have previously had little success.

Microparticulate systems which can encapsulate pharmaceutical agents in order to provide protection in the intestine and regulate their rate of release were described in United States Patent No. 5,352,461. This patent relates to drug delivery systems formed from 2,5-diketo-3,6-di(4-succinylaminobutyl)piperazine, which form particles that are pH sensitive so that at low pH they are stable and protect the encapsulated material from proteolysis, while at high pH they disassemble and release the entrapped pharmaceutical agent. Proteinoid micro-particles are also described, which are claimed to be able to encapsulate agents such as insulin and heparin and protect these molecules from gastric acidity and stomach enzymes. These particles, which are claimed to be of sufficiently small size to pass readily through the stomach wall, and to release the agents into the bloodstream, were proposed in International Patent Publication No. WO 88/01213. Still other pH-titratable particulate systems are described in the work of Bergeron *et al.*, *J. Am. Chem. Soc.* 117: 6658 (1995). These structures are based upon the properties of bis-amide dicarboxylic acids. These particles also share the properties of stability at low pH and instability as pH increases.

International Patent Publication No. WO 96/29991 describes the formation of particles that are based upon polyaminoacids, more particularly polyleucine-glutamate. These particles which are prepared from natural amino acids have the property of controlled particle size and are stable over a wide pH range.

Other structures suitable for oral delivery of peptides and proteins are discussed by Leone-Bay *et al.*, *J. Med Chem.* 39: 2571 (1996); and by Rivera *et al.*, *Pharm. Res.*, 14, 1830-34 (1997). For example, Leone-Bay and his co-workers describe the use of *N*-acetylated, non-α, aromatic amino acids, to promote the absorption of

peptides and proteins. In an analogous system, sodium *N*-[8-(2-hydroxybenzoyl)amino]caprylate has been used to enhance the absorption of heparin.

Unfortunately, there are limitations to the effectiveness of the aforementioned described systems for pharmaceutical delivery according to the prior art, as they often utilize non-natural compounds to enhance oral delivery, and as such these molecules may have undesirable characteristics due to being foreign to the body. A further disadvantage is that most of these delivery systems required complicated chemical syntheses with resultant high costs.

In order to protect the drug from the stomach, or the stomach from the drug, the drug may be included within an enteric coating, whereby the drug is released once it reaches the small intestine. Alternatively, solid dispersions of the drug are milled to produce sub-micron particles with a high surface area for more rapid dissolution. Both the enteric coating and the drug milling processes require complicated, high technology machinery and as such add considerable cost to the delivery of the drug.

Another problem has been the delivery of insoluble and moderately soluble pharmaceutical compounds. Many insoluble and moderately water soluble biologically active agents are readily absorbed in the intestine. But the amount of orally administered biologically active agent that is actually absorbed may be much less than the amount administered. To ensure that effective quantities of the biologically active agent administered reach the circulation, large amounts must be administered. One of the main reasons for the poor absorption of insoluble and moderately soluble biologically active agents is that, once the material reaches the intestine, much of it is not in solution and so it passes down the intestine, and is eventually excreted without being absorbed. When insoluble and moderately biologically active agents do disperse in the intestines, they often have slow and variable dissolution patterns. This leads to significant variation, in a given subject as well as between subjects, with respect to the absorption of a biologically active agent. A need therefore exists for a new system for the encapsulation and delivery of biologically active agents that is suitable for various forms of administration and that solves the foregoing problems.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a new system for oral, nasal, buccal, and transdermal delivery of a range of bioactive agents, insoluble as well as moderately soluble, including but not limited to peptides and proteins.

It is a further object of the present invention to provide a system that overcomes, or at least substantially ameliorates, problems outlined above in relation to pharmaceutical agent delivery.

One embodiment of the present invention is a pharmaceutical composition for biologically active agent delivery comprising a complex, between a carboxylic acid and a biologically active agent, that is stable at acidic pH in solution and unstable at basic pH in solution, with the proviso that the carboxylic acid does not have an amide bond or a non-aromatic nitrogen. In two preferable embodiments, the biologically active agent to be delivered is an organic moiety or a biologically active agent that has a solubility of less than 0.05 moles per liter of water. In another embodiment of the present invention the carboxylic acid serves as a biologically active agent transport and delivery system. Another embodiment of the present invention is a method of producing a carboxylic acid complex for biologically active agent encapsulation. In another embodiment, a method is provided for controlled release, in a patient, of a pharmaceutical agent. The method comprises administering to the patient an effective amount of a composition comprising a pharmaceutical agent entrapped within an acid complex. Yet another embodiment of this invention is a method for formulating a pharmaceutical composition that will deliver insoluble or moderately soluble biologically active agents by dissolving such biologically active agents in a alcohol before encapsulating them with a carboxylic acid. A further embodiment of the present invention is a method of delivering biologically active carboxylic acids.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a graph of the area under the curve (AUC) reduction in serum glucose levels in mg/dl from animals which have received an oral administration of insulin formulated with a carboxylic acid complex.

FIGURE 2 is a graph of the AUC reduction in serum glucose levels in mg/dl from animals which have received an oral administration of insulin formulated with an acid complex.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Throughout the present description, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers, but not the exclusion of any other element or integer or group of elements or integers.

It has been discovered that a pharmaceutical or another, biologically active substance, for oral administration, can be "coated" or "encapsulated" with a carboxylic acid, such that the substance is protected from proteolysis in the stomach and is taken up from the intestine. In particular, the present inventor observed that when animals were fed insulin that had been precipitated with a carboxylic acid complex by a decrease in pH, there was a significant modification of serum glucose levels. This result is most likely due to the carboxylic acids coating and protecting the insulin from the proteolytic environment of the stomach, allowing the insulin to pass safely through the stomach and be absorbed in the small intestines.

In accordance with the present invention, carboxylic acids can be used to coat even a poorly or only moderately soluble biologically active agent, thereby to allow delivery and absorption in the intestines. A poorly or moderately soluble biologically active agent is first dissolved in an alcohol and carboxylic acid solution. This solution is then added to a basic solution, which can then be added to or titrated with an acid

solution, so that the carboxylic acid and active substance complex forms and precipitates out of solution. The precipitant is then administered to a patient. Thus, the active substance can be delivered readily, even if it is insoluble or only moderately soluble. This same method can also be used to formulate biologically active carboxylic acids prior to administration to a patient.

In this context, the term "stable" refers to a precipitated state of the carboxylic acid/active agent complex, which state is sufficiently unchanging so that the complex can be separated, stored, and/or administered to a patient. On the other hand, the term "unstable" connotes a state of dissolution, typically in an aqueous solution.

The term "complex" denotes an aggregation of a precipitated carboxylic acid and a biologically active substance. The terms "coated" and "encapsulated" refer to a biologically active substance precipitated with a carboxylic acid. A "moderately soluble" agent is defined as having a solubility of 0.05 to 0.01 moles per liter, while "insoluble" is less than 0.01 moles per liter. The terms "biologically active agent," "biologically active substance," and "active agent" are all used synonymously. The terms "acid" and "alcohol" refer to pharmaceutically acceptable alcohols and acids, respectively. The term "excipient" denotes a usually inert substance that forms a vehicle for a biologically active vehicle.

The phrase "acidic solution" denotes one having a sufficient concentration of hydronium ions, that is a sufficiently low pH, to protonate carboxylic acids to such an extent that the carboxylic acid precipitates out of solution and forms a stable complex with the biologically active agent that is present. Conversely, a "basic solution" is characterized by a sufficiently low enough concentration of hydronium ions, that is a high pH, to cause enough of the present carboxylic acid to become deprotonated or ionized at its functional carboxyl group so that the carboxylic acid dissolves in an aqueous solution.

Carboxylic Acids

A preferred class of suitable, saturated carboxylic acids for the invention conform to the general formula RCOOH, wherein R is a C_9 to C_{30}, preferably C_9 to C_{20}, straight or branched chained alkyl, cycloalkyl, or cycloalkyalkyl, optionally substituted by a carboxyl, hydroxyl, or carbonyl oxygen. In this class, for example, are decanoic (lauric) acid, undecanoic acid, dodecanoic acid, tetradecanoic (myristic) acid, hexadecanoic (palmitic) acid, octadecanoic (stearic) acid, eicosanoic (arachidic) acid, nonadecanoic acid, 2-hydroxydodecanoic acid, 12-hydrocyclodecanoic acid, 12-hydroxystearic acid, 4-tertbutylcyclohexane carboxylic acid, and 2-hexyldecanoic acid.

Preferred unsaturated carboxylic acids, according to the invention, have the general formula RCOOH, wherein R is a C_9 to C_{30}, preferably C_9 to C_{20}, straight or branched chained alkyl, cycloalkyl, or cycloalkyalkyl, optionally substituted by a carboxyl, hydroxyl, or carbonyl oxygen. Illustrative of these are palmitoleic acid, oleic acid, ricinoleic acid, linoleic acid, arachidonic acid, linolenic acid, gamma-linolenic acid, isanic acid, undecylenic acid, cis-5-dodecenoic acid, 10-undecynoic acid, elaidic acid, vaccenic acid, myristoleic acid, eicosenoic acid, eicosatrienoic acid, eicosapentaenoic acid, docosahexaenoic acid, hydnocarpic acid, retinoic acid, and traumatic acid.

Preferred steroid ring system carboxylic acids, have a steroid ring system and at least one carboxylic acid group. Examples of this class includes fusidic acid, apocholic acid, orthocholic acid, chenodeoxycholic acid, hydroxycholic acid, and ursodeoxycholic acid.

Other carboxylic acids which are suitable for this invention are abietic acid, pimaric acid, butibufen, (p-nonylphenoxy)acetic acid, unoprostone, limaprost, 7-hydroxycoumarin-4-acetic acid, 2-(4-isobutylphenyl)butyric acid, levulinic acid, vernolic acid, 4-butylbenzoic acid, 4-tert-butylbenzoic acid, 5-phenylvaleric acid, 4-(4-methoxyphenyl)-butyric acid, trans-4-pentylcyclo-hexane carboxylic acid, 4-biphenyl carboxylic acid, 4'-hydroxy-4-biphenyl-carboxylic acid, alpha-(terbutyl)hydrocinamic acid, 4-hexylbenzoic acid, 4-hexyloxybenzoic acid, 4-benzoyl benzoic acid, 4-biphenyl acetic acid, benzilic acid, 4-heptyl benzoic acid, 4-heptyloxy benzoic acid, cinnamic acid, 4-ethyl-4-biphenylcarboxylic acid, 4-octylbenzoic acid, 4-octoxybenzoic acid, 4-

benzyloxy-3-methoxyphenyl acetic acid, 4-nonyloxy-benzoic acid, 4-palmitylbenzoic acid, 4-palmitolyl-benzoic acid, and 4-undecyloxy-benzoic acid.

Pursuant to the present invention, a pharmaceutical agent can be incorporated within the carboxylic acid system at the time of its formation, preferably by including the agent within the mixture of components required to produce the formulation.

Forming Carboxylic Acid Complexes

The ratio of moles of carboxylic acid to bioactive agent in the present invention can range from 2:1 to 250:1, preferably from 10:1 to 30:1.

In preparing a carboxylic acid formulation, according to the present invention, the basic solution preferably is added slowly, drop-wise and with stirring, into an acidic solution containing a bioactive agent. During the addition of basic solution, containing the carboxylic acid, to the acidic solution containing the bioactive agent, the latter becomes mildly opalescent and then more and more turbid, finally forming a dense suspension which precipitates gradually, once stirring ceases.

This suspension can be administered while in the acidic solution or can be separated from the liquid and further formulated, with one or more excipients. (The acidic solution also could be combined with one or more excipients, prior to administration.) The suspension can be separated by filtration, evaporation, rotatory evaporation, centrifugation, or decantation, or by any other means known by one skilled in the art. The suspension, in a dried or undried state, then can be combined with one or more excipients.

According to one embodiment of the present invention, the carboxylic acid complex is a composition formulated with the following components: a long-chain, saturated or unsaturated, carboxylic acid dispersed in a weakly basic solution, and a biologically active agent, dispersed in a weakly acidic solution. This composition can be made by titration of one solution into the other to form an acidic solution, which contained the precipitated, encapsulated biologically active agent.

The present invention is described further below with reference to the following, non-limiting examples.

Example 1

General Method for the Synthesis of

Carboxylic Acid Structures That Contain Insulin

Carboxylic acid (CA) is dissolved at 100 mg/ml in ethanol. The AA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 2

Use of Dodecanoic Acid for the Synthesis of

Carboxylic Acid Structures That Contain Insulin

Dodecanoic acid (DDA) is dissolved at 100 mg/ml in ethanol. The DDA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 3

Use of Tetradecanoic Acid for the Synthesis

of Carboxylic Acid Structures Containing Insulin

Tetradecanoic acid (TDA) is dissolved at 100 mg/ml in ethanol. The TDA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 4

Use of Hexadecanoic Acid for the Synthesis of Carboxylic Acid Structures Containing Insulin

Hexadecanoic acid (HDA) is dissolved at 100 mg/ml in ethanol. The HDA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 5

Use of Octadecanoic Acid for the Synthesis of Carboxylic Acid Structures Containing Insulin

Octadecanoic acid (ODA) is dissolved at 100 mg/ml in ethanol. The ODA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 6

Use of Oleic Acid for the Synthesis of Carboxylic Acid Structures Containing Insulin

Oleic acid (OA) is dissolved at 100 mg/ml in ethanol. The OA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 7

Use of Palmitoleic Acid for the Synthesis of
Carboxylic Acid Structures Containing Insulin

Palmitoleic acid (PA) is dissolved at 100 mg/ml in ethanol. The PA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 8

Use of Ricinoleic Acid for the Synthesis of
Carboxylic Acid Structures Containing Insulin

Ricinoleic acid (RA) is dissolved at 100 mg/ml in ethanol. The RA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Example 9

Use of Fusidic Acid for the Synthesis of
Carboxylic Acid Structures Containing Insulin

Fusidic acid (FA) is dissolved at 100 mg/ml in ethanol. The FA solution is then added to 0.25 M K_2CO_3 to give a final concentration of 5 mg/ml. The mixture is thoroughly mixed by vortexing and slowly added to an equal volume of 0.5 M citric acid containing 5 mg/ml insulin. The solution was allowed to stir overnight, and was then stored at 4 °C before use.

Biologically Active Agents and Carboxylic Acid Complexes

As indicated above, the carboxylic acid transport delivery system according to the present invention has special utility for assisting the delivery of pharmaceutical

agents which otherwise would experience a loss of efficacy as a result of instability, inadequate uptake following oral administration. an inappropriate rate of release, and/or insufficient solubility. Accordingly, the pharmaceutical agents comprehended by the present invention particularly include peptide and protein pharmaceuticals that are the subject of proteolytic attack or are unstable at the low pH of the stomach as well as biologically active agents that are insoluble or moderately soluble in an aqueous solution. Therapeutic agents according to the invention can be delivered via oral, nasal, buccal, pulmonary, intravaginally and dermal routes of administration.

In the context of this invention it must be stressed, that the phrase "pharmaceutical agent" or "biologically active agent" is not intended to be limited to peptide and protein pharmaceuticals or insoluble and moderately soluble agents but can include therapeutic, prophylactic or diagnostic agents, and organic moieties whose delivery may be aided by incorporation into carboxylic acid systems. This organic moieties include proteins, peptides, polysaccharides, lipopolysaccharides, lipoproteins, glycoproteins, oligonucleotides, or polynucleotides. Species of DNA and RNA (sense or antisense), antibodies, vaccines as well as chemotherapeutic agents are also contemplated. The phrase "pharmaceutical agent" encompasses simple organic or inorganic compounds, nutritional agents or even imaging agents such as metals, radioactive isotopes, radio-opaque or radiolucent agents.

Examples of traditional chemotherapeutic agents include but are not restricted to hormones, polysaccharides, such as heparin, vasoactive and neuroactive agents, immunomodulating agents, cytotoxic agents, steroids, decongestants, anaesthetics, sedatives, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, anti-epileptics, anti-histamines, anti-hypertensive agents, anti-muscarinic agents, anti-mycobacterial agents, anti-neoplastic agents, immunosuppresants, anti-thyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents. diuretics, dopaminergics (anti-parkinsonian agents), haemostatis, immunological agents, lipid regulating agents,

muscle relaxants, parasympathomimetics, parathyroid calcitonin and bisphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators and zanthines or other agents required to be delivered to a patient for therapeutic, prophylactic or diagnostic purposes.

Potential biologically active agents for peptide and protein delivery include alpha antitrypsin, angiogenesis factor, anakinra, antitumor necrosis factor, atriopeptin, calcitonin, cardiac glycosides, epidermal growth factor, erythropoietin, elastase inhibitor, epoetin alpha, epoetin beta, filgastrim, factor VIII, factor IX, granulocyte colony stimulating factor, hirudin, insulin, interferons, interferon-alpha, interferon-gamma, insulin-like growth factor I, insulin-like growth factor I receptor, insulin-like growth factor II, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, interleukin 12, interleukin 12 p40, interleukin 12 p70, interleukin 13, interleukin 15, interleukin 16, interleukin 17, interleukin 18/IGIF, LHRH analogs, monoclonal antibodies, neuropeptides, oxytocin, plasminogen activator inhibitors, platelet derived growth factor, platelet-derived growth factor A chain, platelet-derived growth factor AA, platelet-derived growth factor AB, platelet-derived growth factor B chain, platelet-derived growth factor BB, sargramostim, somatostatin, superoxide dismutase, stem cell factor, tissue plasminogen activator, thrombopoietin, tumor necrosis factor, vasopressin, and wound healing factor. Other molecules include polysaccharides such as heparin and heparin sulphate.

Additional biologically active agents include 6ckine, amphiregulin, angiogenin, β_2-microglobulin, betacellulin, brain-derived neurotrophic factor, C10, ciliary neurotrophic factor, ciliary neurotrophic factor receptor alpha, CPP32, CRG-2, cytokine-induced neutrophil chemotactic factor 1, cytokine-induced neutrophil chemotactic factor 2 alpha, cytokine-induced neutrophil chemotactic factor 2 beta, cytotoxic t-lymphocyte-associated molecule 4, beta endothelial cell growth factor, endothelin-1, eotaxin, eotaxin-2, epithelial-derived neutrophil attractant 78, erythropoietin receptor, Fas, fibroblast growth factor 4, fibroblast growth factor 5, fibroblast growth factor 6, fibroblast growth factor 7/KGF, fibroblast growth factor 8,

fibroblast growth factor 8b, fibroblast growth factor 8c, fibroblast growth factor 9, fibroblast growth factor acidic, fibroblast growth factor basic, Flt-3 ligand, fractalkine, glial cell line-derived neurotropic factor, granulocyte chemotactic protein, granulocyte colony stimulating factor receptor, granulocyte macrophage colony stimulating factor, growth related protein, growth related protein alpha, growth related protein beta, growth related protein gamma, hemofiltrate CC chemokine 1, heparin binding epidermal growth factor, hepatocyte growth factor, heregulin alpha, heregulin beta 1, I-309, interleukin 1 alpha, interleukin 1 beta, interleukin 1 receptor antagonist, IP-10, JE/MCP-1, KC, keratinocyte growth factor/FGF-7, lactoferrin, leptin, leukemia inhibitory factor, luciferase, macrophage colony stimulating factor, macrophage colony stimulating factor receptor, macrophage inflammatory protein 1 alpha, macrophage inflammatory protein 1 beta, macrophage inflammatory protein 1 gamma, macrophage inflammatory protein 2, macrophage inflammatory protein 3 alpha, macrophage inflammatory protein 3 beta, macrophage migration inhibitory factor, macrophage-derived chemokine, MARC/MCP-3, macrophage stimulating protein, midkine, monocyte chemotactic protein 1/MCAF, monocyte chemotactic protein 2, monocyte chemotactic protein 3, monocyte chemotactic protein 4, monocyte chemotactic protein 5, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, myeloperoxidase, beta nerve growth factor, neurotrophin 3, neurotrophin 4, nitric oxide synthase, oncostatin M, placenta growth factor, placenta growth factor 2, platelet-derived endothelial cell growth factor, pleiotrophin, pre-B cell growth stimulating factor/SDF-1, RANTES, secretory leukocyte protease inhibitor, stromal cell-derived factor 1/PBSF, stromal cell-derived factor 1 alpha/PBSF, stromal cell-derived factor 1 beta/PBSF, thymus and activation-regulated chemokine, thymus-expressed chemokine, transforming growth factor alpha, transforming growth factor beta, transforming growth factor beta 1, transforming growth factor beta 1.2, transforming growth factor beta 2, transforming growth factor beta 3, transforming growth factor beta 5, latency-associated peptide, latent transforming growth factor beta 1, transforming growth factor beta binding protein, tumor necrosis factor alpha, tumor necrosis factor beta, and vascular endothelial growth factor

Biologically active carboxylic agents that can be prepared prior to administration according one of the methods of the present invention include of butibufen, chenodeoxycholic acid, eicosapentaenoic acid, 4-ethyl-4-biphenylcarboxylic acid, fusidic acid, hydnocarpic acid, ibufenac, ibuprofen, limaprost, prostaglandin E1, prostaglandin F2a, retinoic acid, undecylenic acid, and unoprostone.

Insoluble and moderately soluble biologically active agents include 17-pregma-2,4-dien-20-yno-[2,3-d]isoxazol-17-ol(Danazol), 5,17,-1'-(mehtylosulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol(Steroid A), piposulfan, camptothecin, ethyl-3,5-diacetoamido-2,4,6-triiodobenzoate, vitamin E, cyclosporin, propanolol, ibuprofen, fenoprofen, beclomethanzone, beclomethanzone, naproxen, napthalene phenanthrene, 1,4-napthaquinone, 1,2-napthaquinone, griseofulvin, ubidecarenone, dexamethazone, pilocarpine, idarubicin, and anti-inflammatory agents including arthorpathy including diclofenac, fenclofenac, flufenamic acid, fluriprofen, indomethacin, ketoprofen, tolmetin, oxyphenbutazone, phenylbutazone, feprazone, azapropazone, piroxicam, and sulindac.

The category of insoluble and moderately soluble biologically active agents also includes known analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics including penicillins, anticoagulants, antidepressants, antidiabetic agents, anti-epileptics, anti-histamines, anti-hypertensive agents, anti-muscarinic agents, anti-mycobacterial agents, anti-neoplastic agents, immunosuppresants, anti-thyroid agents, antiviral agents, anxiolytic sedatives including hypnotics and neuroleptics, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants including expectorants and mucolytics, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics including anti-parkinsonian agents, haemostatis, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid hormone, calcitonin and bisphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones including steroids, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and zanthines.

The foregoing enumeration of active agents is not intended to be exhaustive. In addition, it should be noted that the pharmaceutical agents according to the invention can be in various forms such as charged or uncharged molecules, components of molecular complexes, salts, amines, ethers, esters. amides or other derivatives or pro-biologically active agents of the agents concerned.

Administering and Treatment with Carboxylic Acid Compositions

Importantly, this invention also relates to a method of controlled biologically active agent release within a patient, which patient is administered a composition comprising a pharmaceutical agent which is entrapped or encapsulated within a carboxylic acid system (CAS) according to the invention. In its broadest sense, this method can be used for the therapy, prophylaxis or diagnosis of any vertebrate animal, although it is preferred that the animal concerned is a mammal. Particularly preferred are laboratory animals such as mice, guinea pigs, rabbits, domestic animals such as cats and dogs, farm animals such as horses, cattle, sheep, goats, pigs, captive wild animals such as lions, tigers, elephants or primates such as humans, chimpanzees, baboons, and apes.

The effective amount of the pharmaceutical agent delivered when delivered in combination within the CAS according to the invention will depend upon numerous factors which would be readily apparent to a person skilled in the art. For example, the type, age and sex of the vertebrate animal concerned, the disorder that the animal is suffering from, or prone to suffer from, the height and weight of the animal and naturally the type of pharmaceutical agent which is being delivered. The dose will also depend upon the stability of the CAS and the level of control over release of the entrapped or encapsulated pharmaceutical agent, which will be related to the nature of the acid carboxylic acid used to form the CAS. When all of these factors are taken into consideration by a person skilled in the art, the appropriate dose can be determined.

It may be necessary for the compositions according to the invention to be administered in conjunction with one or more pharmaceutically suitable carriers and/or excipients. Once again, the nature of the carrier or excipient substance will depend upon numerous factors such as the route of administration, the nature of the cross-

linked particle, and the nature of the pharmaceutical agent concerned. For a complete discussion of appropriate pharmaceutical carriers and excipients, we refer to the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, Second Edition (1994), edited by Ainley Wade and Paul J. Weller, and published by The Pharmaceutical Press (London), the relevant contents of which are incorporated herein by reference. Pharmaceutically acceptable carriers are materials that can be used as a vehicle for administering a medicament because the material is inert or otherwise medically acceptable, as well as compatible with the active agent. A pharmaceutically acceptable carrier can contain conventional additives such as diluents, adjuvants, antioxidants, preservatives and solubilizing agents.

As indicated above, the composition according to the invention can be administered via either enteral or parenteral routes of administration. In the most preferred embodiment of the invention, administration is via the oral route although, for example, rectal administration or direct administration to the stomach or small intestine is also possible. In addition, it is envisaged that the compositions according to the invention also can be administered nasally, buccally, transdermally, optically, aurally, vaginally, topically, pulmonary, or directly into an organ or via other parenteral means. Suitable formulations for administration include aerosols, capsules, creams, lotions, lozenges, ointments, pills, powders, suppositories, syrups, tablets, tinctures, and unguents.

For administration via these means, the composition should be provided in a suitable dosage form with appropriate carriers and/or excipients, as discussed, for example, in the HANDBOOK OF PHARMACEUTICAL EXCIPIENTS, cited above. Suitable excipients include but are not limited to diluents, emulsions, gelatins, liquors, ointments, oleaginous vehicles, solutions and suspensions.

Example 10

Modification of Serum Glucose of Rats
Receiving Carboxylic Acid Structures that Contained Insulin

Male Wistar rats were placed in a restraining apparatus and a blood sample was obtained from the tail vein of the conscious rats. The rats then received by gavage

feeding a 1 mg dose of insulin formulated in CAS. At 60, 120, 180, 240 and 300 minutes following injection the rats were bled from the tail vein. Serum glucose was measured directly from unclotted blood using a Precision QID Medisense™ glucometer. Results are plotted using the glucose values obtained prior to insulin administration (T_0) as indicative of the normal values for each rat. Data from groups of four rats are presented as the mean ± 1 SEM. Data are calculated as the Area Under the Curve (AUC) of reduction in serum glucose levels when compared to the values obtained at T_0.

FIGURE 1 shows a modification of serum glucose levels following oral administration of a 1 mg dose of insulin formulated within CAS. Data is presented as the mean AUC (6 hours) ± 1 SEM. CAS were formed with deoxycholic acid (DOC), decanoic acid (Deca), dodecanoic acid (Dodeca), tetradecanoic acid (Tetradeca), hexadecanoic acid (Hexadeca) or octadecanoic acid (Octadeca), formulated using either 0.5 M citric acid as the acid phase, or 1.5 M acetic acid (Ac), as the acid phase. As can be seen from Figure 1 there was a significant modification of serum glucose when rats were fed insulin incorporated within CAS made of deoxycholic acid (DOC), decanoic acid (Deca), dodecanoic acid (Dodeca), tetradecanoic acid (Tetradeca), hexadecanoic acid (Hexadeca) or octadecanoic acid (Octadeca), formulated using either 0.5 M citric acid as the acid phase, or 1.5 M acetic acid (Ac), as the acid phase.

FIGURE 2 shows a modification of serum glucose levels following oral administration of a 1 mg dose of insulin formulated within CAS. Data is presented as the mean AUC (6 hours) ± 1 SEM. CAS were formed with oleic acid, palmitoleic acid, ricinoleic acid, or fusidic acid, formulated using 0.5 M citric acid as the acid phase. As can be seen from Figure 2 there was a significant modification of serum glucose when rats were fed insulin incorporated within CAS made of oleic acid, plamitoleic acid, ricinoleic acid, or fusidic acid, formulated using 0.5 M citric acid as the acid phase.

It is to be understood that the present invention has been described by way of example only and with reference to a number of preferred embodiments. Modifications and/or alterations to the invention which would be obvious to a person skilled in the art

based upon the disclosure herein, are considered to fall within the intended scope and spirit of the invention.

The respective disclosures of all publication cited above are expressly incorporated by reference in their entireties, to the same extent as if each were incorporated by reference individually.

Claims

1. A pharmaceutical composition comprising a biologically active agent encapsulated by a carboxylic acid that forms a complex that is stable at an acidic pH in solution and unstable at a basic pH in solution, wherein said carboxylic acid does not have an amide bond or a non-aromatic nitrogen.

2. A pharmaceutical composition according to claim 1, wherein said agent is an organic moiety.

3. A pharmaceutical composition according to claim 2, wherein said agent is selected from the group consisting of a protein, a peptide, a polysaccharide, a lipopolysaccharide, a lipoprotein, a glycoprotein, an oligonucleotide, or a polynucleotide.

4. A pharmaceutical composition according to claim 2, wherein said agent has a solubility of less than or equal to 0.05 moles per liter of water.

5. A pharmaceutical composition according to claim 1, said carboxylic acid being a saturated fatty acid of the formula RCOOH, wherein R is a C_9 to C_{30} straight or branch chained alkyl, cycloalkyl, or cycloalkyalkyl, optionally substituted by a carboxyl, hydroxyl, or carbonyl oxygen.

6. A pharmaceutical composition according to claim 5, wherein said saturated fatty acid is selected from the group consisting of decanoic acid, undecanoic acid, dodecanoic acid, tetradecanoic acid, hexadecanoic acid, octadecanoic acid, eicosanoic (arachidic) acid, nonadecanoic acid, 2-hydroxydodecanoic acid, 12-hydrocyclodecanoic acid, 12-hydroxystearic acid, 4-tertbutylcyclohexane carboxylic acid, and 2-hexyldecanoic acid.

7. A pharmaceutical composition according to claim 1, said carboxylic acid being an unsaturated fatty acid having the formula RCOOH, wherein R is a C_9 to C_{30} straight or branch chained alkyl, cycloalkyl, or cycloalkyalkyl, optionally substituted by a carboxyl, hydroxyl, or carbonyl oxygen.

8. A pharmaceutical composition according to claim 7, wherein said unsaturated carboxylic acid is selected from the group consisting of palmitoleic acid, oleic acid, ricinoleic acid, linoleic acid, arachidonic acid, linolenic acid, gamma-linolenic acid, isanic acid, undecylenic acid, cis-5-dodecenoic acid, 10-undecynoic acid, elaidic acid, vaccenic acid, myristoleic acid, eicosenoic acid, eicosatrienoic acid, eicosapentaenoic acid, docosahexaenoic acid, hydnocarpic acid, retinoic acid, and traumatic acid.

9. A pharmaceutical composition according to claim 1, wherein said carboxylic acid has a steroid ring system.

10. A pharmaceutical composition according to claim 9 wherein said steroid ring system carboxylic acid is selected from the group consisting of fusidic acid, apocholic acid, orthocholic acid, chenodeoxycholic acid, hydroxycholic acid, and ursodeoxycholic acid.

11. A pharmaceutical composition according to claim 1, wherein said carboxylic acid is selected from the group consisting of abietic acid, pimaric acid, butibufen, (p-nonylphenoxy)acetic acid, unoprostone, limaprost, 7-hydroxycoumarin-4-acetic acid, 2-(4-isobutylphenyl)butyric acid, levulinic acid, vernolic acid, 4-butylbenzoic acid, 4-tert-butylbenzoic acid, 5-phenylvaleric acid, 4-(4-methoxyphenyl)-butyric acid, trans-4-pentylcyclo-hexane carboxylic acid, 4-biphenyl carboxylic acid, 4'-hydroxy-4-biphenyl-carboxylic acid, alpha-(terbutyl)hydrocinamic acid, 4-hexylbenzoic acid, 4-hexyloxybenzoic acid, 4-benzoyl benzoic acid, 4-biphenyl acetic acid, benzilic acid, 4-heptyl benzoic acid, 4-heptyloxy benzoic acid, cinnamic acid, 4-ethyl-4-biphenylcarboxylic acid, 4-octylbenzoic acid, 4-octoxybenzoic acid, 4-benzyloxy-3-methoxyphenyl acetic acid, 4-nonyloxy-benzoic acid, 4-palmitylbenzoic acid, 4-palmitolyl-benzoic acid, and 4-undecyloxy-benzoic acid.

12. A pharmaceutical composition according to claim 3, wherein said agent is insulin.

13. A pharmaceutical composition according to claim 3, wherein said agent is erythropoietin.

14. A pharmaceutical composition according to claim 3, wherein said agent is granulocyte colony stimulating factor.

15. A pharmaceutical composition according to claim 3, wherein said agent is hirudin.

16. A pharmaceutical composition according to claim 3, wherein said agent is vasopressin.

17. A pharmaceutical composition according to claim 3, wherein said agent is heparin.

18. A method for the preparation of a pharmaceutical composition according to claim 1 comprising:
dissolving said carboxylic acid in a pharmaceutically acceptable alcohol
adding said carboxylic acid solution to a basic solution of suitable pH at which said carboxylic acid is soluble;
adding said carboxylic acid solution to an acidic solution of said biologically active agent, and; stirring such that said carboxylic acid precipitates with said agent, forming a complex.

19. A method according to claim 18, wherein said agent is selected from the group consisting of alpha antitrypsin, angiogenesis factor, anakinra, antitumor necrosis factor, atriopeptin, calcitonin, cardiac glycosides, epidermal growth factor, erythropoietin, elastase inhibitor, epoetin alpha, epoetin beta, filgastrim, factor VIII, factor IX, granulocyte colony stimulating factor, hirudin, insulin, interferons, interferon-alpha, interferon-gamma, insulin-like growth factor I, insulin-like growth factor I receptor, insulin-like growth factor II, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, interleukin 12, interleukin 12 p40, interleukin 12 p70, interleukin 13, interleukin 15, interleukin 16, interleukin 17, interleukin 18/IGIF, LHRH analogs, monoclonal antibodies, neuropeptides, oxytocin, plasminogen activator inhibitors, platelet derived growth factor, platelet-derived growth factor A chain, platelet-derived growth factor AA,

platelet-derived growth factor AB, platelet-derived growth factor B chain, platelet-derived growth factor BB, sargramostim, somatostatin, superoxide dismutase, stem cell factor, tissue plasminogen activator, thrombopoietin, tumor necrosis factor, vasopressin, and wound healing factor.

20. A method for the preparation of a pharmaceutical composition according to claim 1 comprising:
dissolving said carboxylic acid in a pharmaceutically acceptable alcohol;
adding said carboxylic solution to a basic solution of suitable pH at which said carboxylic acid is soluble;
adding an acidic solution of said biologically active agent to said carboxylic solution, and;
stirring such that said carboxylic acid precipitates with said agent, forming a complex.

21. A method according to claim 20, wherein said agent is selected from the group consisting of alpha antitrypsin, angiogenesis factor, anakinra, antitumor necrosis factor, atriopeptin, calcitonin, cardiac glycosides, epidermal growth factor, erythropoietin, elastase inhibitor, epoetin alpha, epoetin beta, filgastrim, factor VIII, factor IX, granulocyte colony stimulating factor, hirudin, insulin, interferons, interferon-alpha, interferon-gamma, insulin-like growth factor I, insulin-like growth factor I receptor, insulin-like growth factor II, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, interleukin 12, interleukin 12 p40, interleukin 12 p70, interleukin 13, interleukin 15, interleukin 16, interleukin 17, interleukin 18/IGIF, LHRH analogs, monoclonal antibodies, neuropeptides, oxytocin, plasminogen activator inhibitors, platelet derived growth factor, platelet-derived growth factor A chain, platelet-derived growth factor AA, platelet-derived growth factor AB, platelet-derived growth factor B chain, platelet-derived growth factor BB, sargramostim, somatostatin, superoxide dismutase, stem cell factor, tissue plasminogen activator, thrombopoietin, tumor necrosis factor, vasopressin, and wound healing factor.

22. A method for treating a patient with a pharmaceutical composition according to claim 1, comprising: administering an effective amount of said complex to patient in need thereof.

23. A method according to claim 22, wherein said agent is selected from the group consisting of alpha antitrypsin, angiogenesis factor, anakinra, antitumor necrosis factor, atriopeptin, calcitonin, cardiac glycosides, epidermal growth factor, erythropoietin, elastase inhibitor, epoetin alpha, epoetin beta, filgastrim, factor VIII, factor IX, granulocyte colony stimulating factor, hirudin, insulin, interferons, interferon-alpha, interferon-gamma, insulin-like growth factor I, insulin-like growth factor I receptor, insulin-like growth factor II, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, interleukin 12, interleukin 12 p40, interleukin 12 p70, interleukin 13, interleukin 15, interleukin 16, interleukin 17, interleukin 18/IGIF, LHRH analogs, monoclonal antibodies, neuropeptides, oxytocin, plasminogen activator inhibitors, platelet derived growth factor, platelet-derived growth factor A chain, platelet-derived growth factor AA, platelet-derived growth factor AB, platelet-derived growth factor B chain, platelet-derived growth factor BB, sargramostim, somatostatin, superoxide dismutase, stem cell factor, tissue plasminogen activator, thrombopoietin, tumor necrosis factor, and wound healing factor.

24. A method according to claim 22, wherein said complex is surrounded by an enteric coating.

25. A composition according to claim 4, wherein said agent selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics including penicillins, anticoagulants, antidepressants, antidiabetic agents, anti-epileptics, ant-histamines, anti-hypertensive agents, anti-muscarinic agents, anti-mycobacterial agents, anti-neoplastic agents, immunosuppresants, anti-thyroid agents, antiviral agents, anxiolytic sedatives including hypnotics and neuroleptics, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants including expectorants and mucolytics, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics including anti-parkinsonian agents, haemostatis, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid hormone, calcitonin and bisphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones including steroids,

anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and zanthines.

26. A pharmaceutical composition according to claim 4, wherein said biologically active agent is selected from the group consisting of 17-pregma-2,4-dien-20-yno-[2,3-d]isoxazol-17-ol(danazol), 5,17,-1'-(mehtylosulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol(steroid A), piposulfan, camptothecin, ethyl-3,5-diacetoamido-2,4,6-triiodobenzoate, vitamin E, cyclosporin, propanolol, ibuprofen, fenoprofen, beclomethanzone, naproxen, naphthalene phenanthrene, 1,4-naphthaquinone, 1,2-napthaquinone, griseofulvin, ubidecarenone, dexamethazone, pilocarpine, idarubicin, and anti-inflammatory agents including arthorpathy including diclofenac, fenclofenac, flufenamic acid, fluriprofen, indomethacin, ketoprofen, tolmetin, oxyphenbutazone, phenylbutazone, feprazone, azapropazone, piroxicam, and sulindac.

27. A pharmaceutical composition according to claim 2, wherein said biologically active agent is selected from the group consisting of alpha antitrypsin, angiogenesis factor, anakinra, antitumor necrosis factor, atriopeptin, calcitonin, cardiac glycosides, epidermal growth factor, erythropoietin, elastase inhibitor, epoetin alpha, epoetin beta, filgastrim, factor VIII, factor IX, granulocyte colony stimulating factor, hirudin, insulin, interferons, interferon-alpha, interferon-gamma, insulin-like growth factor I, insulin-like growth factor I receptor, insulin-like growth factor II, interleukin 2, interleukin 3, interleukin 4, interleukin 5, interleukin 6, interleukin 7, interleukin 8, interleukin 9, interleukin 10, interleukin 11, interleukin 12, interleukin 12 p40, interleukin 12 p70, interleukin 13, interleukin 15, interleukin 16, interleukin 17, interleukin 18/IGIF, LHRH analogs, monoclonal antibodies, neuropeptides, oxytocin, plasminogen activator inhibitors, platelet derived growth factor, platelet-derived growth factor A chain, platelet-derived growth factor AA, platelet-derived growth factor AB, platelet-derived growth factor B chain, platelet-derived growth factor BB, sargramostim, somatostatin, superoxide dismutase, stem cell factor, tissue plasminogen activator, thrombopoietin, tumor necrosis factor, vasopressin, and wound healing factor.

28. A method for the preparation of a pharmaceutical composition according to claim 1, comprising:

dissolving said biologically active agent in a pharmaceutically acceptable alcohol;
dissolving said carboxylic agent in said pharmaceutically acceptable alcohol;
adding said mixture to a suitably basic solution in which said acid is soluble; and
adding said solution containing mixture to an acidic solution and stirring such that said carboxylic agent precipitates with said agent.

29. A method according to claim 28, wherein said agent is selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics including penicillins, anticoagulants, antidepressants, antidiabetic agents, anti-epileptics, ant-histamines, anti-hypertensive agents, anti-muscarinic agents, anti-mycobacterial agents, anti-neoplastic agents, immunosuppresants, anti-thyroid agents, antiviral agents, anxiolytic sedatives including hypnotics and neuroleptics, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants including expectorants and mucolytics, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics including anti-parkinsonian agents, haemostatis, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid hormone, calcitonin and bisphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones including steroids, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and zanthines.

30. A method according to claim 28, wherein said bioactive agent is selected from the group consisting of 17-pregma-2,4-dien-20-yno-[2,3-d]isoxazol-17-ol(danazol), 5,17,-1'-(mehtylosulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol(steroid A), piposulfan, camptothecin, ethyl-3,5-diacetoamido-2,4,6-triiodobenzoate, vitamin E, cyclosporin, propanolol, ibuprofen, fenoprofen. beclomethanzone, naproxen, naphthalene phenanthrene, 1,4-naphthaquinone, 1,2-napthaquinone, griseofulvin, ubidecarenone, dexamethazone, pilocarpine, idarubicin, and anti-inflammatory agents including arthorpathy including diclofenac, fenclofenac, flufenamic acid, fluriprofen, indomethacin, ketoprofen, tolmetin, oxyphenbutazone, phenylbutazone, feprazone, azapropazone, piroxicam, and sulindac.

31. A method according to claim 28, wherein said complex is surrounded by an enteric coating.

32. A pharmaceutical composition according to claim 2, wherein said biologically active agent is selected from the group consisting of 6ckine, amphiregulin, angiogenin, β_2-microglobulin, betacellulin, brain-derived neurotrophic factor, C10, ciliary neurotrophic factor, ciliary neurotrophic factor receptor alpha, CPP32, CRG-2, cytokine-induced neutrophil chemotactic factor 1, cytokine-induced neutrophil chemotactic factor 2 alpha, cytokine-induced neutrophil chemotactic factor 2 beta, cytotoxic t-lymphocyte-associated molecule 4, beta endothelial cell growth factor, endothelin-1, eotaxin, eotaxin-2, epithelial-derived neutrophil attractant 78, erythropoietin receptor, Fas, fibroblast growth factor 4, fibroblast growth factor 5, fibroblast growth factor 6, fibroblast growth factor 7/KGF, fibroblast growth factor 8, fibroblast growth factor 8b, fibroblast growth factor 8c, fibroblast growth factor 9, fibroblast growth factor acidic, fibroblast growth factor basic, Flt-3 ligand, fractalkine, glial cell line-derived neurotropic factor, granulocyte chemotactic protein, granulocyte colony stimulating factor receptor, granulocyte macrophage colony stimulating factor, growth related protein, growth related protein alpha, growth related protein beta, growth related protein gamma, hemofiltrate CC chemokine 1, heparin binding epidermal growth factor, hepatocyte growth factor, heregulin alpha, heregulin beta 1, I-309, interleukin 1 alpha, interleukin 1 beta, interleukin 1 receptor antagonist, IP-10, JE/MCP-1, KC, keratinocyte growth factor/FGF-7, lactoferrin, leptin, leukemia inhibitory factor. luciferase, macrophage colony stimulating factor, macrophage colony stimulating factor receptor, macrophage inflammatory protein 1 alpha, macrophage inflammatory protein 1 beta, macrophage inflammatory protein 1 gamma, macrophage inflammatory protein 2, macrophage inflammatory protein 3 alpha, macrophage inflammatory protein 3 beta, macrophage migration inhibitory factor, macrophage-derived chemokine, MARC/MCP-3, macrophage stimulating protein, midkine, monocyte chemotactic protein 1/MCAF, monocyte chemotactic protein 2, monocyte chemotactic protein 3, monocyte chemotactic protein 4, monocyte chemotactic protein 5, MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, myeloperoxidase, beta nerve growth factor, neurotrophin 3, neurotrophin 4, nitric oxide synthase, oncostatin M, placenta growth factor, placenta growth factor 2, platelet-derived endothelial cell growth factor, pleiotrophin, pre-B cell growth stimulating factor/SDF-1, RANTES, secretory

leukocyte protease inhibitor, stromal cell-derived factor 1/PBSF, stromal cell-derived factor 1 alpha/PBSF, stromal cell-derived factor 1 beta/PBSF, thymus and activation-regulated chemokine, thymus-expressed chemokine, transforming growth factor alpha, transforming growth factor beta, transforming growth factor beta 1, transforming growth factor beta 1.2, transforming growth factor beta 2, transforming growth factor beta 3, transforming growth factor beta 5, latency-associated peptide, latent transforming growth factor beta 1, transforming growth factor beta binding protein, tumor necrosis factor alpha, tumor necrosis factor beta, and vascular endothelial growth factor.

33. A method for the preparation of a pharmaceutical composition, comprising:

selecting a biologically active carboxylic acid that forms a complex which is stable at an acidic pH in solution and unstable at a basic pH in solution,

dissolving said biologically active carboxylic acid in a pharmaceutically acceptable alcohol;

dissolving said carboxylic acid in said pharmaceutically acceptable alcohol;

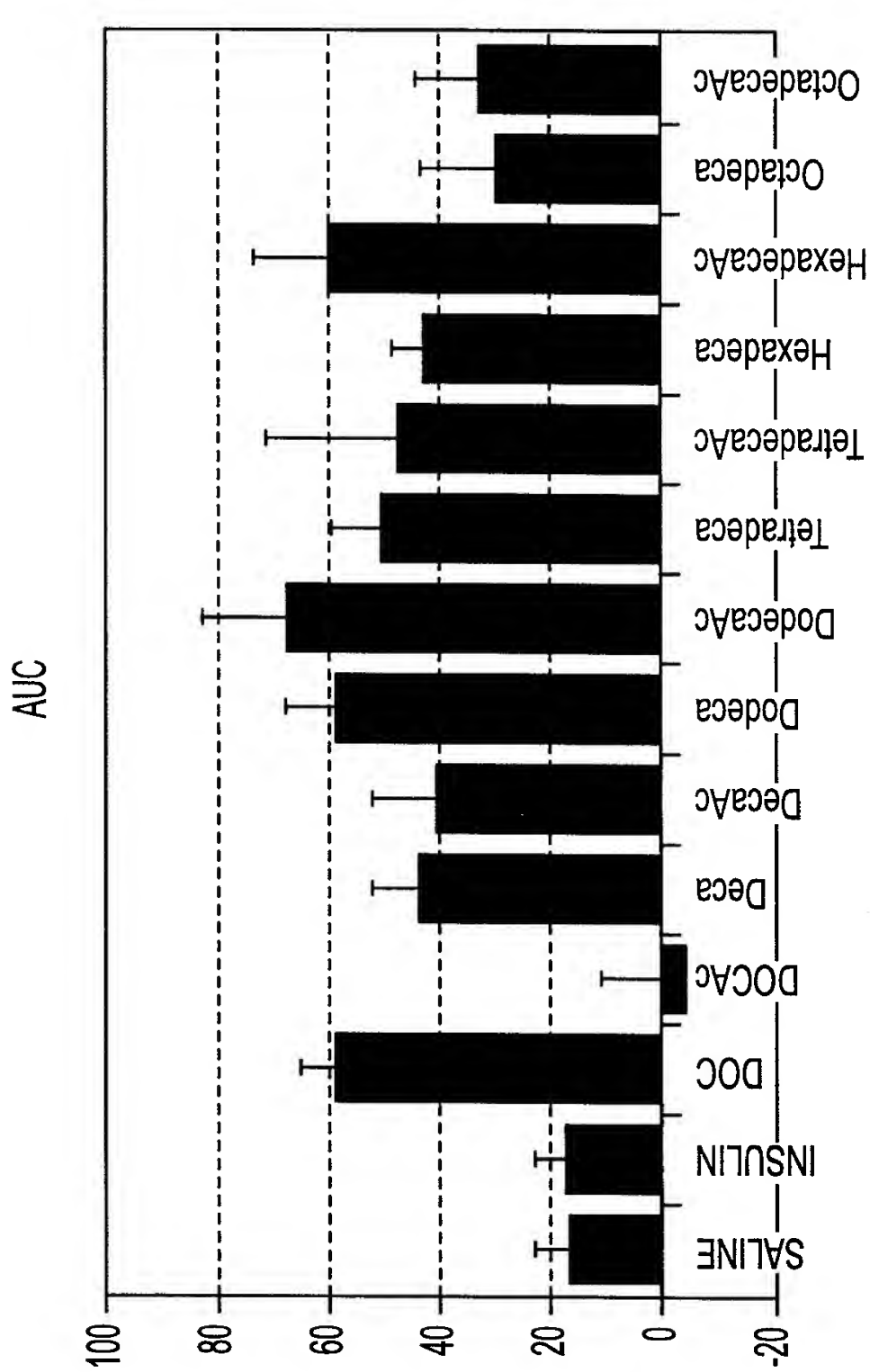
adding said mixture to a suitably basic solution in which said acid is soluble; and

adding said solution containing mixture to an acidic solution and stirring such that said carboxylic acid precipitates.

34. The method according to claim 33 wherein said carboxylic acid is selected from the group consisting of butibufen, chenodeoxycholic acid, eicosapentaenoic acid, 4-ethyl-4-biphenylcarboxylic acid, fusidic acid, hydnocarpic acid, ibufenac, ibuprofen, limaprost, prostaglandin E1, prostaglandin F2a, retinoic acid, undecylenic acid, and unoprostone.

35. A pharmaceutical composition according to claim 1, wherein said composition further comprises at least one excipient.

36. A pharmaceutical composition according to claim 1, wherein said composition formulated as an aerosol, a capsule, a cream, a lotion, a lozenge, an ointment, a pill, a powder, a suppository, a syrup, a tablet, a tincture, or an unguent.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80
60
40
20
0
-20
SALINE
INSULIN
DOC
DOCAc
Deca
DecaAc
Dodeca
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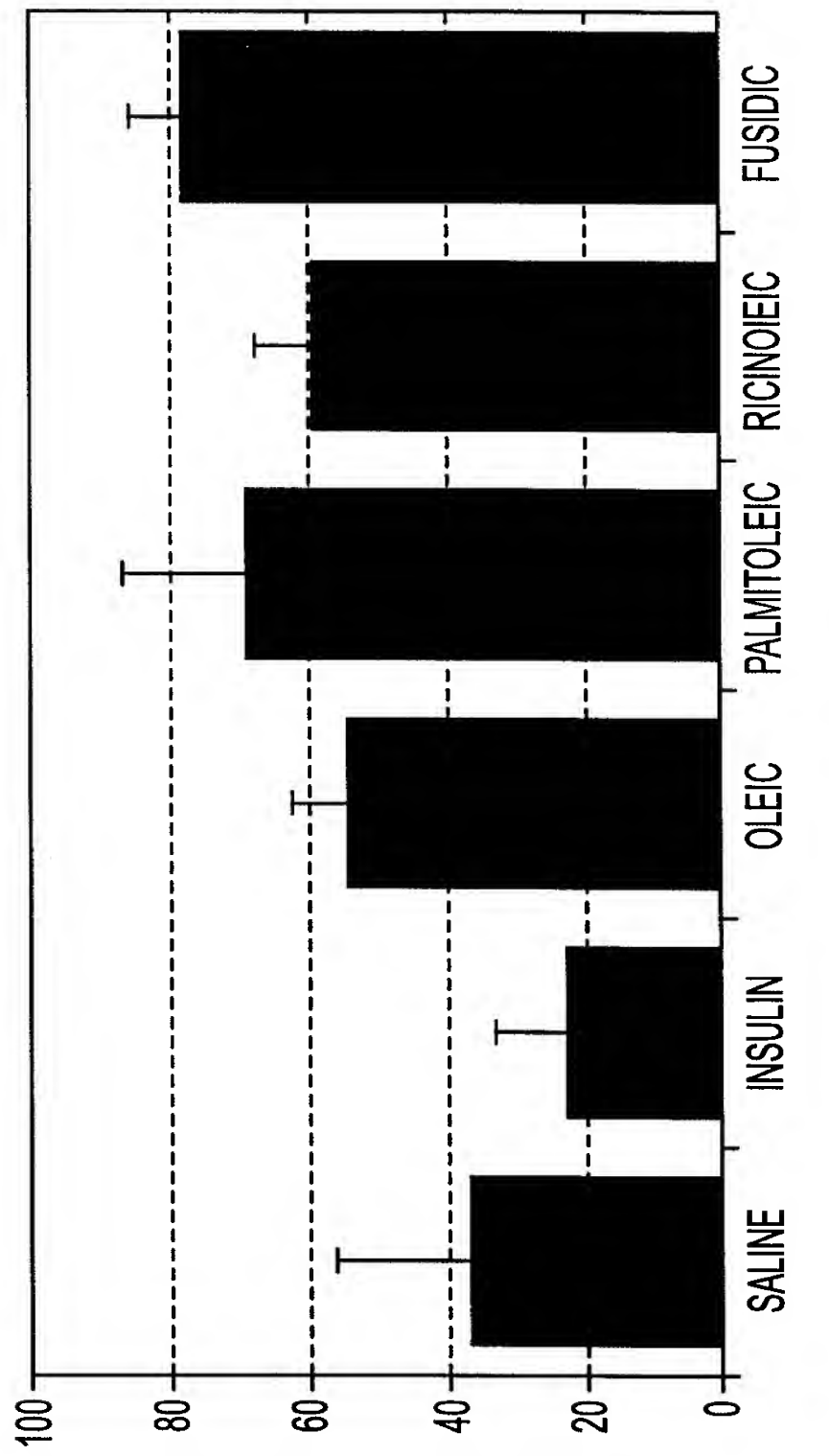
OctadecaAc

FIG. 1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80
60
40
20
0
SALINE
INSULIN
OLEIC
PALMITOLEIC
RICINOIEIC
FUSIDIC
PREPARATION

FIG. 2